

# Total synthesis of (–)-microcarpalide, a novel microfilament disrupting metabolite †

Paolo Davoli,\* Alberto Spaggiari, Luca Castagnetti and Fabio Prati\*

Dipartimento di Chimica, Università di Modena e Reggio Emilia, via Campi 183, I-41100 Modena, Italy. E-mail: davoli.chemistry@unimo.it; prati.fabio@unimo.it

Received 25th July 2003, Accepted 15th October 2003

First published as an Advance Article on the web 6th November 2003

The stereoselective total synthesis of (–)-microcarpalide, a recently discovered 10-membered lactone of fungal origin displaying a remarkable disrupting action on actin microfilaments, was accomplished by using ring-closing metathesis (RCM) as the key step for the formation of the medium-sized ring. The diene ester required for the macrocyclization reaction was assembled *via* DCC-mediated esterification of two suitable partners, each bearing a terminal alkene group. The alcohol fragment was synthesized from *n*-bromohexane through a seven-step sequence entailing two consecutive stereoselective homologations of chiral boronic esters as strategic transformations for the sequential insertion of the two stereocentres with the final *S* absolute configuration, using (+)-pinanediol as the chiral director; final elaboration to the desired C<sub>11</sub> framework envisaged treatment with an allyl Grignard reagent and oxidative cleavage of the boronic scaffold. In contrast, the acidic fragment was prepared in ten steps from D-tartaric acid, whose C<sub>4</sub> backbone was elongated to the required C<sub>7</sub> skeleton by means of two distinct Swern–Wittig oxidation–homologation sequences.

## Introduction

Secondary metabolites from endophytic fungi have been receiving a great deal of attention in recent years, and a number of peculiar structures with specific bioactivities have been discovered so far.<sup>1,2</sup>

Along this line, microcarpalide (**1**) has been recently characterised as a new secondary metabolite produced by an endophytic fungus (as yet unidentified) isolated from the bark of the tropical tree *Ficus microcarpa* L.<sup>3</sup> Bioassay-guided purification of fermentation broths using immunofluorescence microscopy to test anticytoskeletal activity led to the isolation of a new substance displaying a remarkable disrupting action on actin microfilaments, to which the structure **1** was assigned (Fig. 1).<sup>3</sup>

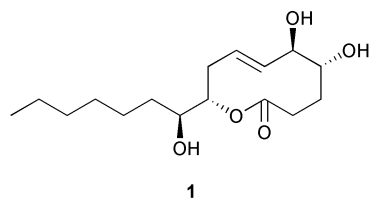
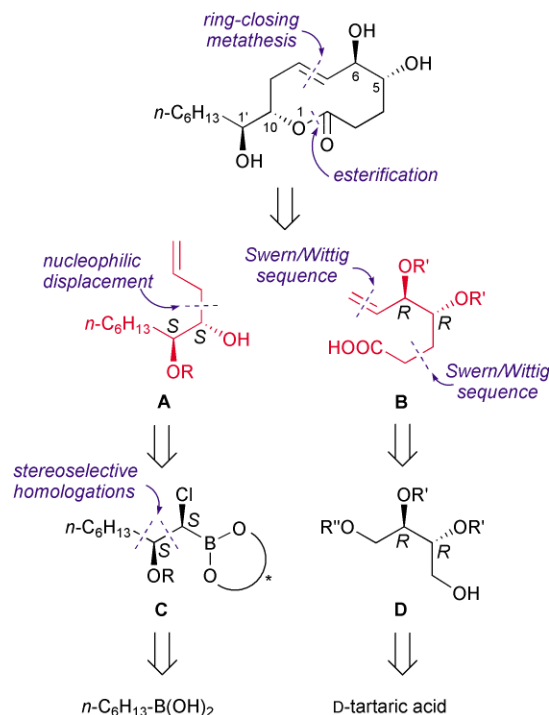


Fig. 1

Microcarpalide represents a novel alkyl-substituted nonenolide structurally related to a family of phytotoxins such as achaetolide,<sup>4</sup> pinolidoxin,<sup>5</sup> lethalotoxin,<sup>6</sup> putaminoxins<sup>7</sup> and herbarumins,<sup>8</sup> from which it differs in the hydroxylation pattern and the double bond position within the 10-membered lactone, as well as in the longer side chain at C-10. At concentrations of 0.5–1 μg mL<sup>-1</sup>, microcarpalide was found to disrupt actin microfilaments in approximately 50% of A-10 cells (from rat smooth muscle);<sup>3</sup> moreover, it displayed a weak cytotoxicity to mammalian cells,<sup>3</sup> thus making it an attractive tool for studying cell motility and metastasis, and a potential lead structure to develop new anticancer drugs.

Owing to such a peculiar biological activity and attracted by the structural potential of microcarpalide for structure–activity

relationship studies, we decided to challenge its total synthesis. In this respect, aiming also at shedding light on the mechanism of action of this novel fungal metabolite, the synthetic route ought to be versatile enough to allow the preparation of analogues thereof. With this in mind, the retrosynthetic approach outlined in Scheme 1 was devised.



Scheme 1 Retrosynthetic analysis.

Firstly, the macrocyclic framework of microcarpalide was retrosynthetically disassembled into fragments **A** and **B** (Scheme 1) by means of two key disconnections, namely a ring-closing metathesis (RCM)<sup>9</sup> for the construction of the oxecin ring, and an esterification reaction for assembling the two alkene fragments. Both fragments contain two stereogenic

† Electronic supplementary information (ESI) available: <sup>1</sup>H and <sup>13</sup>C NMR spectra of synthetic microcarpalide (**1**). See <http://www.rsc.org/suppdata/ob/b3/b308709c/>

carbon atoms and bear a terminal alkene group that is required for the RCM macrocyclization.

Fragment **A** represents a dihydroxy substituted 1-undecene with *S* absolute configuration at both adjacent stereocentres (C-10 and C-1' in **1**) and can be ultimately disconnected to the C<sub>6</sub> alkyl boronic acid (Scheme 1). In fact, boronic ester chemistry provides a highly stereoselective method for the sequential insertion of stereocentres into the C–B bond.<sup>10</sup> In particular, chain elongation by means of two strategic stereoselective homologations of the corresponding (+)-pinanediol ester would allow installation of the C-1' and C-10 atoms with the desired stereochemistry under the guide of the same chiral director, thus affording chloro derivative **C**. Final insertion of the allylic appendage *via* S<sub>N</sub>2 displacement and oxidative removal of the boronic ester would then lead to the required C<sub>11</sub> skeleton of **A**, providing at the same time the free hydroxy group at C-10 to be used for the coupling reaction with partner **B**.

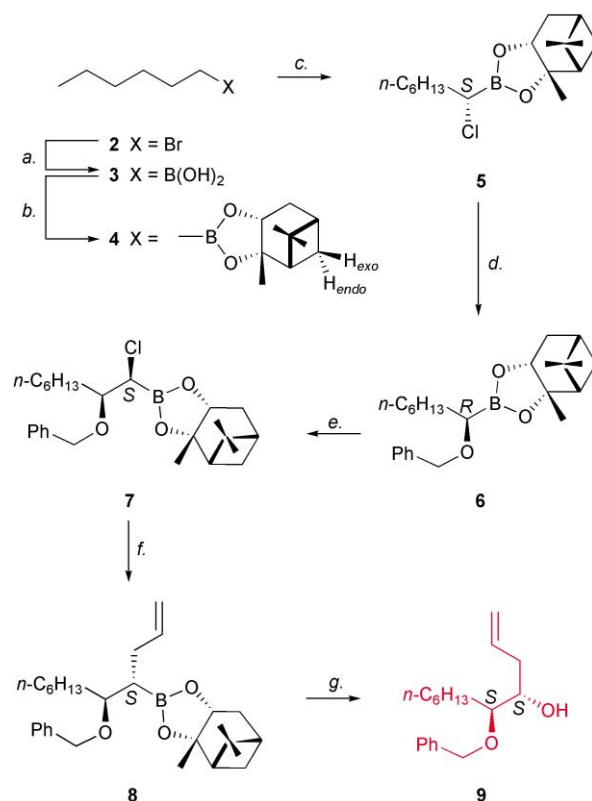
Fragment **B** is a 4,5-disubstituted 6-heptenoic acid bearing two contiguous hydroxy groups in a *threo* fashion, whose *R* absolute configurations can be matched by the pattern displayed by D-tartaric acid. Retrosynthetically, the C<sub>7</sub> backbone was traced back to a suitably protected D-threitol **D** (Scheme 1) by use of two different Swern–Wittig oxidation–homologation sequences (each one with an appropriate phosphorus ylide), which would allow chain elongation at both termini of the C<sub>4</sub> chiral synthon **D**. In turn, threitol derivative **D** can be easily prepared from D-tartaric acid, as reported in the literature for the L-enantiomer.

## Results and discussion

### Synthesis of fragment A

For our synthesis we envisaged using the stereoselective homologation of chiral boronic esters developed by Matteson and coworkers<sup>10</sup> to install the two adjacent stereocentres with the required *S* absolute configuration. In particular, (+)-pinanediol was chosen as the chiral auxiliary to direct the stereochemical outcome of the homologation reaction; in fact, the (+) isomer is known to induce the *S* configuration when used as the chiral director.<sup>10,11</sup>

The synthetic approach to fragment **A** commenced from commercially available *n*-bromohexane (**2**), which was converted into the corresponding Grignard derivative; reaction between *n*-hexylmagnesium bromide and trimethyl borate in diethyl ether at –78 °C, followed by acidic work-up, furnished boronic acid **3** on a multigram scale in 72% yield (Scheme 2);<sup>12</sup> acid **3** undergoes spontaneous dehydration to form the corresponding trimeric boroxine, as shown by MS analysis. Esterification with the chiral auxiliary (+)-pinanediol in dry Et<sub>2</sub>O at rt readily afforded the corresponding boronate **4** (71% yield).<sup>10</sup> The presence of a carbon–boron bond was confirmed on the basis of the <sup>13</sup>C NMR spectrum displaying a diagnostic broad signal at 10.5 ppm for C-1, which could be detected only in highly concentrated samples. Chiral boronate **4** is an air-stable liquid that can be easily handled and stored over time on the lab shelf.<sup>10</sup> Hence, the stage was set to exploit Matteson's asymmetric homologation for inserting the first stereocentre. Addition of *in situ*-generated (dichloromethyl)lithium to chiral boronic ester **4** at –100 °C in THF<sup>13</sup> provided  $\alpha$ -chloro derivative **5** in good yield (64%) and high diastereoisomeric excess (*d.e.*  $\geq$  98%) (Scheme 2). The presence of a new signal at 3.48 ppm in the <sup>1</sup>H NMR spectrum indicated the successful insertion of a chlorine-bearing carbon atom into the C–B bond of **4**, whereas the diastereoselectivity of the homologation was determined by means of the diagnostic signal of the H<sub>endo</sub> proton of the pinanyl moiety (1.19 ppm, doublet).<sup>11</sup> Since (+)-pinanediol is reported to direct the formation of (*S*)- $\alpha$ -chloroboronic esters,<sup>10,11</sup> the *S* absolute configuration could be

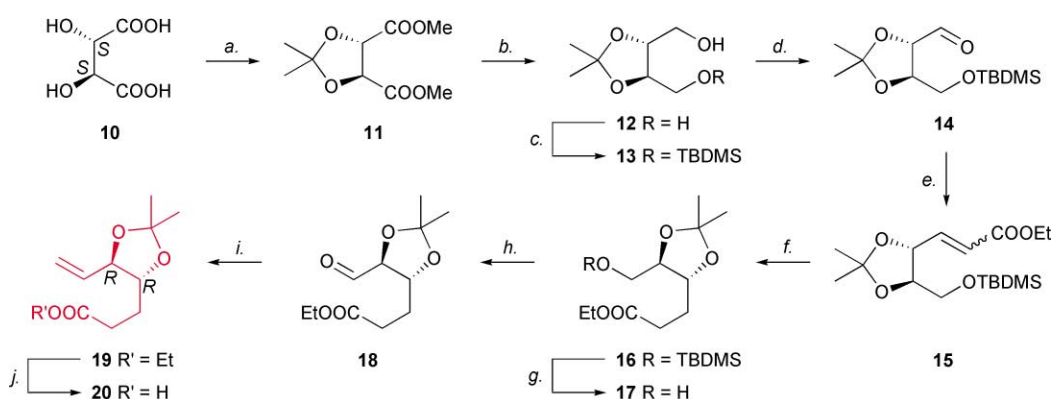


**Scheme 2** Synthesis of fragment **A**. *Reagents and conditions:* a. Mg, Et<sub>2</sub>O, reflux, then trimethyl borate, –78 °C  $\rightarrow$  rt, 72%; b. (1*S*,2*S*,3*R*,5*S*)-(+)-pinanediol, Et<sub>2</sub>O, rt, 71%; c. (dichloromethyl)lithium, THF, –100 °C  $\rightarrow$  rt, 64%; d. benzyl alcohol, *n*-BuLi, THF, –78 °C  $\rightarrow$  rt, then reflux, 70%; e. (dichloromethyl)lithium, ZnCl<sub>2</sub>, THF, –100 °C  $\rightarrow$  rt, 61%; f. allylmagnesium bromide, THF, –78 °C  $\rightarrow$  rt, 74%; g. H<sub>2</sub>O<sub>2</sub>, NaOH, THF, 0 °C  $\rightarrow$  45 °C, 90%.

assigned to 1-chloroheptaneboronate **5**. Subsequently, exposure to a solution of (benzyloxy)lithium (prepared by titration of benzyl alcohol with *n*-butyllithium in the presence of 1,10-phenanthroline as indicator) in THF resulted in the S<sub>N</sub>2 nucleophilic displacement of the chlorine atom,<sup>11</sup> thus affording the corresponding 1-benzyloxy derivative **6** in 70% yield (Scheme 2). Compound **6** bears a protected hydroxy group with *R* absolute configuration,<sup>14</sup> which corresponds to the desired 1'*S* stereochemistry in **1**. More interestingly, benzyl ether **6** could be also obtained directly from **4** through a one-pot procedure that avoided the isolation of the  $\alpha$ -chloroboronic ester **5** and, gratifyingly, proceeded with higher overall yield (55%).

By close analogy, the second asymmetric centre was introduced sequentially through stereoselective homologation of  $\alpha$ -benzyloxy boronic ester **6**. Addition of (dichloromethyl)lithium at –100 °C in THF,<sup>13</sup> followed by treatment with zinc chloride (1 M solution in Et<sub>2</sub>O)<sup>10</sup> provided 2-benzyloxy-1-chloroboronic ester **7** in good yield (61%) (Scheme 2). In the absence of zinc chloride, the homologation reaction was found to display incomplete conversion and proceeded in lower yield, albeit with excellent diastereoselectivity. In contrast, addition of zinc chloride resulted in better conversions and yield, without affecting *d.e.* NMR spectroscopy confirmed the insertion of a new carbon atom ( $\delta_{\text{H}}$  3.65 ppm, doublet;  $\delta_{\text{C}}$  46.1 ppm, broad signal due to the C–B bond) and the H<sub>endo</sub> proton was used again as diastereotopic marker to assess *d.e.*, which was found to be greater than 98%. By use of the same chiral director, the *S* absolute configuration was installed.

The desired C<sub>11</sub> backbone of fragment **A** was then constructed by exploiting the ease of reaction of  $\alpha$ -halo boronic esters with C-nucleophiles, namely Grignard reagents.<sup>10</sup> In the case of 1-chlorooctaneboronate **7**, an allylic appendage was required for such a purpose. Accordingly, a solution of **7** in THF was reacted with allylmagnesium bromide at –78 °C,



**Scheme 3** Synthesis of fragment **B**. *Reagents and conditions*: a. 2,2-dimethoxypropane, *p*-TsOH, reflux, 91%; b. LAH, Et<sub>2</sub>O, reflux, 87%; c. TBDMSCl, NaH, THF, 91%; d. Swern oxidation (oxalyl chloride–DMSO, CH<sub>2</sub>Cl<sub>2</sub>, triethylamine, –70 °C), 90%; e. (ethoxycarbonylmethylene)triphenylphosphorane, DMF, rt, 94%; f. H<sub>2</sub>, Pd/C, EtOH, rt, 99%; g. TBAF, THF, rt, 82%; h. Swern oxidation (oxalyl chloride–DMSO, CH<sub>2</sub>Cl<sub>2</sub>, triethylamine, –72 °C), 76%; i. methyltriphenylphosphonium bromide, *n*-BuLi, THF, –20 °C → rt, 42%; j. KOH, THF–MeOH–water, rt, 81%.

affording compound **8** in 74% yield (Scheme 2). Since nucleophilic displacements on  $\alpha$ -chloroboronates are known to occur with S<sub>N</sub>2 mechanism,<sup>14</sup> alkene **8** has opposite configuration at the boron-bearing C atom with respect to **7** (even though the same *S* chiral descriptor is used for priority reasons). Hence, boronic ester **8** already features the two adjacent asymmetric centres with the correct final stereochemistry required by **1**. Finally, oxidative removal of the boronic scaffold by treatment with basic hydrogen peroxide in THF,<sup>10,11,15</sup> which is reported to occur with retention of configuration,<sup>16</sup> yielded the desired alcohol **9** (90%) with *S,S* absolute configuration (Scheme 2), thus releasing the free hydroxy function required for the coupling reaction with fragment **B** and meanwhile retaining the benzylic protection at the adjacent position (the C-1'-to-be in **1**) to be cleaved off only at the end of the overall sequence.

### Synthesis of fragment B

For the preparation of the acidic partner **B**, we devised using D-tartaric acid as the starting chiral synthon, to which a number of transformations described in the literature for the corresponding L-enantiomer were applied.

Firstly, D-(–)-tartaric acid (**10**) was refluxed with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid to yield the corresponding dimethyl ester acetonide **11** in excellent yield (Scheme 3).<sup>17</sup> Subsequent lithium aluminium hydride reduction in diethyl ether gave D-(–)-threitol acetonide **12** (87% yield),<sup>18</sup> which was treated with sodium hydride in THF and reacted with *tert*-butyldimethylsilyl chloride at rt to afford the monosilylated derivative **13** on a multigram scale in excellent yield (91%) (Scheme 3).<sup>19</sup>

Alcohol **13** was oxidised to aldehyde **14** under Swern conditions at –70 °C;<sup>20–22</sup> <sup>1</sup>H NMR analysis of the crude residue revealed the presence of the diagnostic proton at 9.78 ppm as a doublet, thus confirming the identity of the product, which was used without further purification for the next Wittig reaction. Homologation of **14** with (ethoxycarbonylmethylene)triphenylphosphorane in anhydrous DMF at rt<sup>22</sup> smoothly afforded alkene **15** as an 85 : 15 *trans*–*cis* mixture in 85% combined yield (over two steps) (Scheme 3); separation of the geometric isomers was not required since the newly formed double bond was to be hydrogenated in the following step. Catalytic hydrogenation of alkene **15** with 10% palladium on charcoal in ethanol under H<sub>2</sub> atmosphere furnished hexanoate **16** in quantitative yield.<sup>23</sup> Subsequently, removal of the TBDMS protecting group with tetra-*n*-butylammonium fluoride in dry THF at rt<sup>24</sup> provided alcohol **17** in excellent yield (82%), thus releasing the hydroxy function at C-6 to be used for the final chain elongation, yet again by means of a Swern–Wittig sequence. Oxidation of **17** in the presence of oxalyl chloride–DMSO in dry CH<sub>2</sub>Cl<sub>2</sub> at –72 °C, followed by

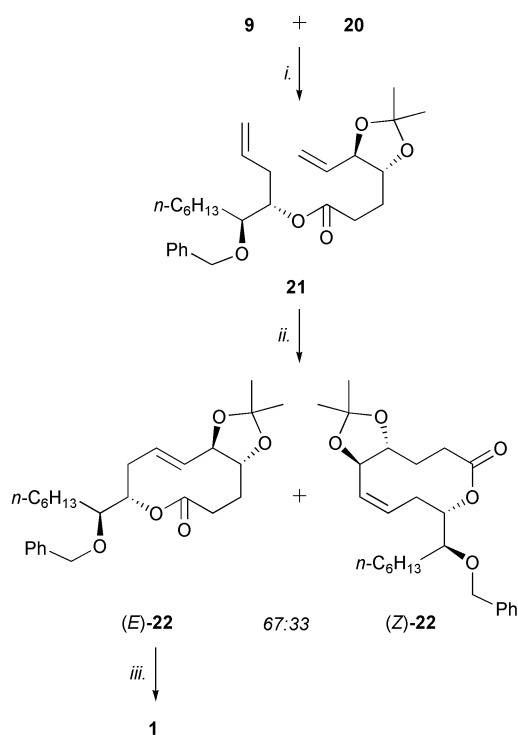
treatment with triethylamine,<sup>20–22</sup> gave aldehyde **18** (76%) which was immediately homologated with methylenetriphenylphosphorane in THF at –20 °C to provide 6-heptenoate derivative **19** in 42% yield (Scheme 3).<sup>25</sup> Batty and Crich used buffered pyridinium chlorochromate (PCC) oxidation to prepare the (4*S*,5*R*) enantiomer of the L-threitol-derived aldehyde **18** in order to avoid migration of the isopropylidene group to the 5,6 site, which they experienced on the *erythro* analogue using other oxidation methods, including Swern's.<sup>25</sup> In contrast, however, we did not observe any 5,6-isopropylidene shift during Swern oxidation of either alcohol **13** or **17**, and both could be converted into the desired aldehyde **14** and **18**, respectively. Saponification of the ester **19** with KOH in THF–MeOH–water (2 : 2 : 1) afforded the desired free acid **20** in 81% yield,<sup>25</sup> which was directly employed for the next coupling step with alcohol **9**.

### Completion of the total synthesis

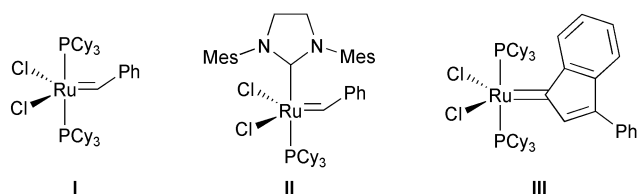
With the two alkene partners in hand, assembly of the dienic substrate for the crucial macrocyclization reaction *via* ring-closing metathesis (RCM)<sup>9</sup> was performed by coupling alcohol **9** to acid **20** with DCC in the presence of DMAP in diethyl ether at rt, to give ester **21** in 85% yield (Scheme 4). A highly-diluted solution (0.45 mM) of diene **21** in anhydrous degassed dichloromethane was then refluxed for 48 h under argon atmosphere in the presence of Grubbs' catalyst **I** (17 mol %) (Fig. 2),<sup>9</sup> to afford the 10-membered lactone **22** in excellent yield (92%) as a mixture of two geometric isomers in a 67 : 33 *E*–*Z*-ratio (Scheme 4). The desired *trans*-oxecin (*E*)-**22** could be separated by column chromatography from the *cis*-analogue (*Z*)-**22**; the stereochemistry of the newly formed double bond was unambiguously assigned by comparison of the *J*<sub>7–8</sub> coupling constants (15.6 against 10.3 Hz, respectively).

The same stereoselectivity in the RCM cyclization has been also reported by Marco and coworkers in the course of the first total synthesis of microcarpalide,<sup>26</sup> by using a closely related diene ester that only differed in the protection at 1'-OH, whereas formation of the unwanted (*Z*)-olefin resulted upon exposure to second-generation Grubbs' catalyst **II** (Fig. 2).

The lack of stereocontrol in the synthesis of medium-sized rings by RCM has been repeatedly addressed in the literature (for leading references, see ref. 27) and still represents a major drawback of this reaction. Mixtures of (*E*) and (*Z*) cycloalkenes are usually formed and, in addition, 8- to 11-membered rings are sensitive to the reverse process (ROM or ROMP) because of their intrinsic ring strain.<sup>27</sup> Therefore, a reliable and general method of controlling the geometry of the newly formed double bond in RCM macrocyclizations has been called for. In this respect, second-generation Grubbs' catalyst **II** is



**Scheme 4** Completion of the total synthesis. *Reagents and conditions:* *i.*, DCC, DMAP, Et<sub>2</sub>O, rt, 85%; *ii.*, Grubbs' catalyst **I**, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 92%; *iii.*, TiCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 66%.



**Fig. 2** Catalysts for ring-closing metathesis (RCM): **I** Grubbs' catalyst; **II** 2<sup>nd</sup> generation Grubbs' catalyst; **III** Fürstner's catalyst.

known to favour the formation of the thermodynamically more stable (*Z*)-isomers.<sup>27</sup>

Within 10-membered lactones, for instance, in the total synthesis of pinolidoxin by Liu and Kozmin, the presence of an acetonide group spanning the two hydroxy functions in positions  $\alpha$  and  $\beta$  to one of the alkene appendages was found to result in the stereoselective formation of the undesired (*Z*)-olefin in the key RCM step with catalyst **II**, whereas removal of the acetonide prior to metathetic ring closure determined a loss of stereocontrol in double bond formation.<sup>28</sup> Similarly, but opposite in sense, excellent stereoselectivity in RCM was reported by Fürstner's group in the course of their recent total synthesis of herbarumins and pinolidoxin,<sup>27</sup> a family of phyto-toxic nonenolides related to **1**, by using the newly developed ruthenium indenylidene catalyst **III**<sup>29</sup> (Fig. 2). In particular, the stereocontrol of the key RCM macrocyclization was successfully reversed by simply switching to ruthenium complex **III**, resulting in the selective formation of the desired (*E*)-olefin in a 10 : 1 ratio with the (*Z*)-isomer, which, in contrast, was formed exclusively when carbene **II** was employed as the catalyst.<sup>27</sup>

Prompted by such promising performances, we also exposed diene **21** to a catalytic amount of Fürstner's complex **III**,<sup>29</sup> under similar reaction conditions. Although compound **21** was successfully metathesized to lactone **22**, unfortunately the reaction afforded a mixture of (*E*) and (*Z*) isomers in about 2 : 1 ratio, respectively, as determined on the basis of <sup>1</sup>H NMR analysis, by using the signal belonging to H-7 [for (*E*)-olefin: 5.32 ppm, doublet of doublets; for (*Z*): 5.50 ppm, triplet] as diagnostic marker.

In contrast, the most recent total synthesis of microcarpalide by Gurjar *et al.* featured an RCM reaction with Grubbs' catalyst **I** which proceeded with excellent stereoselectivity (10 : 1), yielding almost exclusively the required (*E*)-alkene from a diene ester similar to **21**, except for the presence of two benzyl groups protecting the hydroxyls at positions 5 and 6, as well as for a methoxyethoxymethyl substituent at 1'-OH.<sup>30</sup> Hence, the nature of the diene substrate that is subjected to the RCM reaction, and especially of its appendages, seems to play an important role in determining the stereochemical outcome of the metathetic process, at least for 10-membered lactones, thus making it difficult to draw up general rules for controlling selectivity in RCM reactions, even within a given catalyst.

Treatment of (*E*)-**22** with titanium tetrachloride in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C<sup>30-31</sup> (Scheme 4) resulted in the simultaneous removal of both protective groups, affording a single product whose spectral data matched perfectly those reported by Hemscheidt<sup>3</sup> for the natural compound. Like natural microcarpalide, when dissolved in acetonitrile synthetic **1** appears as a mixture of two slowly interconverting conformers in a 76 : 24 ratio, as determined from the <sup>1</sup>H NMR spectrum by using signals which displayed suitable separation, namely those for H-10 (4.84 ppm for the major conformer and 4.63 ppm for the minor one) and, in addition, 5-OH (3.09 and 3.19 ppm, respectively). This conformer ratio is identical to the 3.5 : 1 value described in the literature for the natural **1** in the same solvent.<sup>3</sup>

At present, only two total syntheses of microcarpalide have been disclosed in the literature so far.<sup>26,30</sup> Like ours, both rely on the construction of the 10-membered skeleton by means of a ring-closing metathesis (RCM) macrocyclization using Grubbs' catalyst **I** as the crucial step, thus requiring the synthesis of two alkene partners, namely **A** and **B** (Scheme 1). Subunit **B** was always prepared from the chiral pool, by starting either from D-tartaric acid<sup>26</sup> or D-mannose;<sup>30</sup> the latter, however, required a cumbersome and unduly lengthy sequence, thus making the tartrate-derived one more attractive and applicable, even though a more straightforward and, possibly, enantioselective approach would be desirable for future developments. As far as partner **A** is concerned, it was previously synthesized by means of diastereoselective addition of an allyl tin reagent to an (*R*)-glycidol-derived aldehyde as the key step<sup>26</sup> or, later,<sup>30</sup> through asymmetric dihydroxylation of a suitable alkene precursor, followed by a long sequence of transformations. In contrast, here a completely different and original route to fragment **A** was followed, which fully exploited the stereoselective homologation of chiral boronic esters<sup>10</sup> as a powerful tool to introduce sequentially stereocentres with high diastereoselectivity and desired absolute stereochemistry by use of the same chiral auxiliary.

## Conclusions

In summary, a new stereoselective total synthesis of the microfilament disrupting agent microcarpalide (**1**), a secondary metabolite produced by an endophytic fungus, has been accomplished. Formation of the required 10-membered lactone was achieved by means of ring-closing metathesis (RCM) of a suitable diene ester that was assembled by coupling the two advanced fragments **A** and **B** (*i.e.* **9** and **20**, respectively). Fragment **A** has been synthesized in 7 steps from *n*-bromohexane through two consecutive stereoselective homologations of chiral boronic esters **4** and **6** as key transformations, which allowed the sequential introduction of the two asymmetric centres with the final *S* absolute configuration, using (+)-pinanediol as the chiral auxiliary. Final elaboration entailed insertion of the allylic appendage on derivative **7** by nucleophilic displacement of the chlorine atom, followed by oxidative removal of the boronic scaffold to reveal alcohol **9**. In turn, fragment **B** has been prepared in 10 steps from D-(–)-tartaric acid. The required C<sub>7</sub> backbone of **20** has been constructed

from the C<sub>4</sub> starting synthon using two different Swern–Wittig oxidation–homologation sequences as key steps, each one with a suitable phosphorus ylide. Hence, D-tartrate-derived monosilylated threitol **13** was oxidized and homologated to afford alkene **15**, which was hydrogenated and exposed to TBAF, thus revealing alcohol **17**. Swern oxidation and Wittig methylenation furnished ester **19**, whose saponification yielded 6-heptenoic acid **20**. Completion of the total synthesis entailed a DCC-mediated coupling between partners **9** and **20**, followed by RCM using Grubbs' catalyst **I**, providing the desired 10-membered macrocyclic framework with good stereoselectivity (67 : 33 *E-Z*) and excellent yield. Finally, cleavage of protective groups afforded a single product whose spectroscopic properties were identical with those of the natural compound **1**.

With a view to future structure–activity relationship (SAR) studies, the synthetic route to **1** herein disclosed appears flexible enough to allow the preparation of microcarpalide analogues, by simply varying the starting materials and/or the chiral director employed. In particular, our total synthesis features an original enantioselective approach to fragment **A** that allows the asymmetric insertion of suitably labelled atoms in specific positions by means of Matteson's stereoselective homologation, thus making available labelled derivatives which could be of value for shedding light on the mechanism of action of this novel fungal metabolite endowed with such a peculiar biological activity. Further applications of this methodology toward the preparation of analogues for SAR studies are being currently pursued in our laboratory and will be reported in due course.

## Experimental

### General

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> solution (unless otherwise noted) on a Bruker DPX 200 or AMQ 400 MHz spectrometer; chemical shifts are reported in  $\delta$  values from TMS as internal standard; coupling constants (*J*) are given in Hz. For mass spectral determinations a Finnigan MAT S50 A and a Hewlett Packard HP5989A mass spectrometer were used (EI, 70 eV). Elemental analyses were performed with a Carlo Erba Elemental Analyzer 1110. Optical rotations were recorded in chloroform (unless stated otherwise) at 20 °C on a Perkin-Elmer 241 polarimeter and are in 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup>. All organic solvents were dried and distilled by standard methods prior to use and all reactions requiring anhydrous conditions were carried out using oven-dried and argon-flushed glassware. Chromatographic purification of compounds was performed on silica gel (particle size 0.05–0.20 mm). Analytical TLC was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Merck, Kieselgel 60, F<sub>254</sub>). Compounds were visualized by exposure to UV light, I<sub>2</sub> vapours and by dipping the plates in 1% Ce(SO<sub>4</sub>)<sub>2</sub>·4H<sub>2</sub>O, 2.5% (NH<sub>4</sub>)<sub>2</sub>MoO<sub>7</sub>·4H<sub>2</sub>O in 10% sulfuric acid followed by heating on a hot plate. (1*S*,2*S*,3*R*,5*S*)-(+)-Pinanediol and all other reagents were obtained from Aldrich. Grubbs' catalyst **I** was purchased from Strem Chemicals Ltd., whereas dichloro(3-phenyl-1*H*-inden-1-ylidene)bis(tricyclohexylphosphine)ruthenium(IV) (Fürstner's catalyst, **III**) was prepared according to Fürstner *et al.*<sup>29</sup>

### Synthesis of fragment A

**Hexaneboronic acid (3)**<sup>12,32,33</sup>. Activated magnesium turnings (4.03 g, 16.58 mmol) were suspended in anhydrous diethyl ether (5 mL) in a 100-mL two-necked round bottom flask equipped with a reflux condenser and a dropping funnel. A portion of neat 1-bromohexane (0.4 mL, 2.85 mmol) was added straightaway along with a few crystals of I<sub>2</sub> in order to initiate the reaction. Once the mixture was refluxing, the remaining halide (1.3 mL, 9.25 mmol) dissolved in Et<sub>2</sub>O (3 mL) was added dropwise, and the reaction was kept under gentle reflux for

about 50 min. In a separate flask, trimethyl borate (1.41 mL, 12.10 mmol) was dissolved in the same solvent (8 mL), and the milky solution of *n*-hexylmagnesium bromide was slowly added *via* syringe at –78 °C under mechanical stirring and Ar atmosphere over 10 min, washing with a further 2 mL of ether; during addition, the temperature rose and was carefully maintained below –60 °C. The reaction mixture was stirred overnight and left to cool to rt, affording a light yellowish precipitate. After dilution with Et<sub>2</sub>O (20 mL), the mixture was cooled at 0 °C and 10% aqueous sulfuric acid (12 mL) was added dropwise; the clear solution thus obtained was warmed and stirred for 20 min at rt. The yellow ethereal phase was separated and the aqueous layer extracted with ether (3 × 12 mL); the white emulsion that formed initially upon separation was subjected to the same extraction protocol. The organic phases were pooled, washed with water and brine, and dried over MgSO<sub>4</sub>. Filtration and concentration *in vacuo* afforded the title compound **3** (5.69 g, 72%) as a white solid (mp 68–71 °C) (lit.<sup>12,32,33</sup> 88–90 °C) which was used as such in the following step without further purification. <sup>1</sup>H NMR (200 MHz, as the corresponding boroxine):  $\delta$  0.79–1.00 (5H, m, CH<sub>2</sub>B and CH<sub>3</sub>), 1.22–1.53 (8H, m, 4 × CH<sub>2</sub>). <sup>13</sup>C NMR:  $\delta$  14.3, 23.0, 25.9, 30.0, 32.0 (CH<sub>2</sub>B not seen). MS, *m/z* (as boroxine): 336 (M<sup>+</sup>, 75%), 306 (26), 278 (20), 265 (80), 250 (5), 195 (56), 167 (30), 84 (100), 69 (35), 55 (60). [Found: C, 64.3; H, 11.6. C<sub>18</sub>H<sub>39</sub>B<sub>3</sub>O<sub>3</sub> (boroxine) requires: C, 64.4; H, 11.7%].

**(+)-Pinanediol hexaneboronate (4)**. Boronic acid **3** (920 mg, 7.08 mmol) was dissolved in anhydrous diethyl ether (10 mL) and stirred at rt in the presence of (1*S*,2*S*,3*R*,5*S*)-(+)-pinanediol (1.21 g, 7.08 mmol), which was added portionwise over 1 h 15 min, until TLC analysis (light petroleum–ethyl acetate 80 : 20) showed no disappearance of the pinanediol itself. After rotary evaporation under reduced pressure, the desired ester **4** was separated from the unreacted pinanediol by means of column chromatography (light petroleum–ethyl acetate 80 : 20), affording 1.002 g (71%) of a colourless oil (bp 80 °C, 0.09 mbar), [ $\alpha$ ]<sub>D</sub> +20.9 (*c* 0.90). <sup>1</sup>H NMR (200 MHz):  $\delta$  0.78–0.95 (8H, m, 3 × *H*-6, 2 × CH<sub>2</sub>B and pinanyl CH<sub>3</sub>), 1.15 (1H, d, *J* 12.3, pinanyl *H*<sub>endo</sub>), 1.24–1.56 (14H, m, *H*-2 to *H*-5 and 2 × pinanyl CH<sub>3</sub>), 1.80–2.45 (5H, m, pinanyl protons), 4.27 (1H, dd, *J* 8.6, 1.8, pinanyl *CHOB*). <sup>13</sup>C NMR:  $\delta$  10.5 (m, BCH<sub>2</sub>), 14.4, 22.9, 24.3, 24.5, 26.8, 27.5, 29.1, 30.1, 32.0, 32.5, 36.0, 38.5, 40.0, 51.8, 77.9, 85.6. MS, *m/z*: 264 (M<sup>+</sup>, 11%), 249 (48), 235 (3), 223 (26), 195 (67), 181 (20), 168 (59), 134 (69), 109 (31), 83 (90), 67 (100), 55 (95). (Found: C, 72.7; H, 11.0. C<sub>16</sub>H<sub>29</sub>BO<sub>2</sub> requires: C, 72.7; H, 11.1%).

**(+)-Pinanediol (1*S*)-1-chloroheptaneboronate (5)**. A solution of anhydrous methylene chloride (183  $\mu$ L, 2.85 mmol) in freshly distilled dry THF (4 mL) was cooled at –100 °C and treated with a 2.5 M solution of *n*-BuLi in hexanes (912  $\mu$ L, 2.28 mmol) under Ar flow and mechanical stirring; *n*-BuLi addition took place over a 10 min period and the reaction mixture was then stirred for an additional 30 min, carefully maintaining the temperature below –100 °C. A white precipitate formed, which slowly faded. Pinanediol ester **4** (500 mg, 1.90 mmol) was dissolved in THF (3 mL) and slowly added dropwise to the (dichloromethyl)lithium solution at –100 °C. The reaction mixture was stirred under argon atmosphere and allowed to warm to rt overnight. After rotary evaporation, the residue was diluted with light petroleum (100 mL) and treated with saturated NH<sub>4</sub>Cl (25 mL). The aqueous phase was extracted with light petroleum (2 × 50 mL), the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Column chromatography on SiO<sub>2</sub> using light petroleum–diethyl ether 97 : 3 as the eluant gave homology product **5** (380 mg, 64%) as a clear yellow liquid, [ $\alpha$ ]<sub>D</sub> +27.3 (*c* 0.87). <sup>1</sup>H NMR (200 MHz):  $\delta$  0.88–0.94 (6H, m, 3 × *H*-7 and pinanyl CH<sub>3</sub>), 1.19 (1H, d, *J* 10.9, pinanyl *H*<sub>endo</sub>), 1.24–1.56

(16H, m, *H*-2 to *H*-6 and 2 × pinanyl  $CH_3$ ), 1.80–2.45 (5H, m, pinanyl protons), 3.48 (1H, dd, *J* 7.7, 6.8, *H*-1), 4.38 (1H, dd, *J* 8.8, 2.0, pinanyl *CHOB*).  $^{13}C$  NMR:  $\delta$  14.4, 23.0, 24.3, 26.7, 27.4, 27.6, 28.8, 29.1, 31.8, 34.6, 35.7, 38.6, 39.8, 51.6, 78.9, 87.0 (ClCHB not seen). MS, *m/z*: 312 ( $M^+$ , 3%), 297 (4), 217 (32), 199 (40), 173 (36), 158 (43), 145 (100), 134 (98), 118 (78), 96 (52), 83 (70), 67 (54), 55 (57). (Found: C, 65.2; H, 9.7.  $C_{17}H_{30}BClO_2$  requires: C, 65.3; H, 9.7%).

**(+)-Pinanediol (1*R*)-1-benzyloxyheptaneboronate (6).** Benzyl alcohol (759  $\mu$ L, 7.34 mmol) was dissolved in anhydrous THF (6 mL) in a 25-mL flask equipped with a dropping funnel and a reflux condenser, and a few crystals of oven-dried (110 °C, 20 min) 1,10-phenanthroline were introduced. The solution was cooled at  $-78$  °C and a 2.5 M solution of *n*-BuLi in hexanes (3.22 mL, 8.00 mmol) was added until the mixture turned dark red. After stirring for 15 min at  $-78$  °C and for an additional 5 min at rt under argon flow, chloro derivative **5** (2.081 g, 6.67 mmol) in 6 mL THF was slowly added *via* syringe to the reaction flask at  $-78$  °C. The pale yellow solution thus obtained was allowed to warm to rt overnight under Ar atmosphere. Complete conversion was reached after gentle refluxing of the reaction mixture for 2 h. After dilution with  $Et_2O$  (1 : 1 v/v with respect to THF) and treatment with saturated  $NH_4Cl$  (10 mL), the organic phase was separated and the aqueous layer extracted with ether (3 × 60 mL). The organic phases were pooled, dried ( $Na_2SO_4$ ), filtered and rotary evaporated *in vacuo*. The residue was purified by chromatography (light petroleum–diethyl ether 95 : 5), affording benzyloxy derivative **6** as a fruit-scented bright yellow oil (1.75 g, 70%),  $[a]_D +4.8$  (*c* 2.4). In separate experiments, the title compound **6** was also prepared on a gram scale directly from boronate **4** in a total 55% yield (over two steps), following an improved one-pot procedure that did not require isolation of the intermediate chloro derivative **5**.  $^1H$  NMR (200 MHz):  $\delta$  0.86 (3H, s, pinanyl  $CH_3$ ), 0.89 (3H, t, *J* 5.5, 3 × *H*-7), 1.17 (1H, d, *J* 10.8, pinanyl  $H_{endo}$ ), 1.24–1.52 (16H, m, *H*-2 to *H*-6 and 2 × pinanyl  $CH_3$ ), 1.62–2.45 (5H, m, pinanyl protons), 3.36 (1H, t, *J* 6.4, *H*-1), 4.33 (1H, dd, *J* 8.8, 2.0, pinanyl *CHOB*), 4.52 (1H, d, *J* 12.1,  $CH_2Ph$ ), 4.62 (1H, d, *J* 12.1,  $CH_2Ph$ ), 7.19–7.42 (5H, m, arom).  $^{13}C$  NMR:  $\delta$  14.4, 23.0, 24.4, 26.9, 27.4, 29.1, 29.8, 31.8, 32.2, 35.8, 38.5, 39.9, 51.6, 68.3 (br, CHB), 72.5, 78.5, 86.5, 127.6, 128.2, 128.5, 139.6. MS, *m/z*: 384 ( $M^+$ , 4%), 297 (6), 235 (7), 135 (61), 107 (25), 97 (43), 91 (100), 69 (17), 55 (43). (Found: C, 74.8; H, 9.6.  $C_{24}H_{37}BO_3$  requires: C, 75.0; H, 9.7%).

**(+)-Pinanediol (1*S*,2*S*)-2-benzyloxy-1-chlorooctaneboronate (7).** By close analogy to the synthesis of **5** reported above, (dichloromethyl)lithium was prepared by treatment of dichloromethane (158  $\mu$ L, 2.46 mmol) in THF (4 mL) with *n*-BuLi (2.5 M solution in hexanes, 676  $\mu$ L, 1.64 mmol) at  $-100$  °C. Benzyl ether **6** (591 mg, 1.54 mmol) in THF (4 mL) was then added to such a mixture at  $-100$  °C, and after 5 min a 1 M solution of  $ZnCl_2$  in diethyl ether (923  $\mu$ L, 0.92 mmol) was slowly dropped in. The reaction was stirred under Ar atmosphere and left to warm to rt overnight. The clear and colourless solution thus obtained was concentrated under reduced pressure, diluted with light petroleum (40 mL) and treated with saturated  $NH_4Cl$  (10 mL). After separation of the organic layer, the aqueous phase was extracted with light petroleum (3 × 15 mL), and the organic phases were pooled, dried over  $MgSO_4$ , filtered and rotary evaporated. After chromatographic purification (light petroleum–diethyl ether 95 : 5), the title compound **7** was obtained as a pale yellow liquid (374 mg, 61%),  $[a]_D +7.7$  (*c* 2.3).  $^1H$  NMR (200 MHz):  $\delta$  0.83–0.95 (6H, m, 3 × *H*-8 and pinanyl  $CH_3$ ), 1.17 (1H, d, *J* 10.8, pinanyl  $H_{endo}$ ), 1.27–1.48 (16H, m, *H*-3 to *H*-7 and 2 × pinanyl  $CH_3$ ), 1.60–2.45 (5H, m, pinanyl protons), 3.65 (1H, d, *J* 6.5, *H*-1), 3.81 (1H, dt, *J* 5.3, 6.5, *H*-2), 4.38 (1H, dd, *J* 8.8, 2.0, pinanyl *CHOB*), 4.62 (1H, d, *J* 12.0,  $CH_2Ph$ ), 4.72

(1H, d, *J* 12.0,  $CH_2Ph$ ), 7.20–7.45 (5H, m, arom).  $^{13}C$  NMR:  $\delta$  14.4, 23.0, 24.3, 25.8, 26.7, 26.8, 28.8, 29.6, 32.1, 32.5, 35.6, 38.5, 39.8, 46.1 (br,  $CHCl$ ), 51.6, 72.9, 78.9, 80.9, 87.2, 127.6, 128.1, 128.5, 139.0. MS, *m/z*: 324 ( $[M - PhCH_2OH]^+$ , 30%), 309 (100), 293 (2), 247 (4), 147 (3), 133 (5), 119 (10), 91 (6). (Found: C, 69.6; H, 8.9.  $C_{25}H_{38}BClO_3$  requires: C, 69.4; H, 8.8%).

**(+)-Pinanediol (1*S*,1'*S*)-1-(1'-benzyloxy)heptylbut-3-eneboronate (8).** A 1 M solution of allylmagnesium bromide in diethyl ether (1.88 mL, 1.88 mmol) was slowly added *via* syringe over 10 min to a stirred solution of chloro derivative **7** (730 mg, 1.71 mmol) in anhydrous THF (20 mL) at  $-78$  °C under Ar flow. The mixture was warmed to rt overnight, and a white precipitate began to form while the temperature was rising. The yellow solution was then diluted with light petroleum (20 mL), treated with saturated  $NH_4Cl$  (20 mL) and the organic phase was separated and dried over  $MgSO_4$ . Filtration and concentration *in vacuo* afforded an oily residue which was purified by chromatography (light petroleum–diethyl ether 95 : 5) to give **8** as a pale yellow oil (575 mg, 74%),  $[a]_D +12.7$  (*c* 4.4).  $^1H$  NMR (200 MHz):  $\delta$  0.83 (3H, s, pinanyl  $CH_3$ ), 0.89 (3H, t, *J* 6.3, *H*-7'), 1.20 (1H, d, *J* 10.1, pinanyl  $H_{endo}$ ), 1.24–1.45 (16H, m, *H*-2' to *H*-6' and 2 × pinanyl  $CH_3$ ), 1.50–2.40 (8H, m, *H*-1, *H*-2 and pinanyl protons), 3.58 (1H, q, *J* 5.5, *H*-1'), 4.26 (1H, dd, *J* 8.8, 2.0, pinanyl *CHOB*), 4.53 (2H, AB system, *J* 11.2,  $CH_2Ph$ ), 4.90–5.09 (2H, m, *H*-4), 5.88 (1H, ddt, *J* 16.9, 10.1, 6.5, *H*-3), 7.18–7.40 (5H, m, arom).  $^{13}C$  NMR:  $\delta$  14.4, 23.0, 24.4, 25.8, 26.7, 27.5, 29.1, 29.8, 31.7, 32.2, 33.1, 35.9, 38.5, 39.9, 51.6, 71.3, 78.0, 81.2, 85.8, 115.0, 127.4, 127.9, 128.4, 139.4, 139.7. The EIMS was unobtainable. (Found: C, 76.8; H, 9.8.  $C_{28}H_{43}BO_3$  requires: C, 76.7; H, 9.9%).

**(4*S*,5*S*)-5-Benzyloxyundec-1-en-4-ol (9).** Allyl boronate **8** (50 mg, 0.11 mmol) was dissolved in THF (2 mL) and treated with a 2.2 M solution of NaOH (152  $\mu$ L, 0.34 mmol) at 0 °C for 10 min under magnetic stirring. 35% Hydrogen peroxide (34  $\mu$ L, 0.30 mmol) was added at 0 °C and the mixture was stirred for 15 min, during which a yellow precipitate formed. The reaction was then warmed to 45 °C and the milky solution stirred for an additional 1.5 h, until TLC analysis (light petroleum–diethyl ether 95 : 5) showed disappearance of the starting material. After addition of diethyl ether (15 mL) and water (5 mL), the organic layer was separated and dried over  $MgSO_4$ . Purification of the bright yellow residue obtained upon filtration and rotary evaporation was achieved by column chromatography, using light petroleum–diethyl ether 70 : 30 as the eluant, thus affording the title compound **9** as a colourless liquid (39 mg, 90%),  $[a]_D +17.8$  (*c* 1.5), which upon refrigeration slowly crystallised in transparent needles.  $^1H$  NMR (200 MHz):  $\delta$  0.90 (3H, t, *J* 6.7, *H*-11), 1.22–1.81 (10H, m, *H*-6 to *H*-10), 2.15–2.45 (3H, m, *OH* and *H*-3), 3.34 (1H, q, *J* 5.5, *H*-5), 3.56–3.72 (1H, m, *H*-4), 4.52 (1H, d, *J* 11.3,  $CH_2Ph$ ), 4.67 (1H, d, *J* 11.3,  $CH_2Ph$ ), 5.04–5.16 (2H, m, *H*-1), 5.87 (1H, ddt, *J* 17.6, 9.6, 7.0, *H*-2), 7.24–7.40 (5H, m, arom).  $^{13}C$  NMR:  $\delta$  14.4, 22.9, 25.5, 29.9, 30.6, 32.1, 38.5, 72.4, 72.8, 81.8, 117.6, 128.1, 128.2, 128.8, 135.4, 140.1. MS, *m/z* (as the corresponding TMS ether, by treatment *in situ* with neat MSTFA at 70 °C for 1 h): 333 ( $[M - 15]^+$ , 0.5%), 307 (5), 241 (0.6), 205 (6), 152 (6), 143 (44), 91 (100), 73 (29). (Found: C, 78.2; H, 10.1.  $C_{18}H_{28}O_2$  requires: C, 78.2; H, 10.2%).

## Synthesis of fragment B

**Dimethyl 2,3-*O*-isopropylidene-D-(+)-tartrate (11).** The title compound was prepared in 91% yield on a 50-g scale from commercial D-(–)-tartaric acid (**10**) according to Carmack and Kelley;<sup>17</sup>  $[a]_D +42.0$  (neat) [lit.,<sup>17</sup> (L-isomer)  $-49.4$ ].

**2,3-*O*-Isopropylidene-D-(–)-threitol (12)<sup>34</sup>.** LAH (10.11 g, 0.266 mol) was slurried in dry ether (100 mL) and refluxed for 30 min. Dimethyl 2,3-*O*-isopropylidene-D-(+)-tartrate (**11**)

(28.742 g, 0.132 mol) was dissolved in dry ether (130 mL) and slowly added at rt under vigorous magnetic stirring. The reaction mixture was refluxed for about 3 h and stirred at rt overnight. After cooling with ice, ethyl acetate (12 mL) was carefully added dropwise, followed by water (10 mL, cautiously!), 4 M NaOH (10 mL) and, again, water (30 mL); the suspension was stirred until gas release ceased and the conspicuous ivory precipitate which had settled down was filtered off, washing with abundant ether. The filter cake was extracted thoroughly and repeatedly with ether in a Soxhlet apparatus, and the pooled ethereal extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Claisen distillation of the residue afforded D-threitol derivative **12** (18.6 g, 87%) as a pale yellow dense oil, bp 94–96 °C (0.7 mmHg), [ $\alpha$ ]<sub>D</sub> –2.1 (*c* 2.6) (lit.,<sup>34</sup> –3.1), which crystallised upon freezing. <sup>1</sup>H NMR (200 MHz):  $\delta$  1.36 (6H, s, 2 × CH<sub>3</sub>), 3.40 (2 × 1H, br, 2 × OH), 3.67 (4H, br, 2 × CH<sub>2</sub>), 3.89 (2H, m, 2 × CH). <sup>13</sup>C NMR:  $\delta$  27.3, 62.6, 78.8, 109.6. MS, *m/z* (as the corresponding bisTMS ether, by derivatisation *in situ* with neat MSTFA at 100 °C for 3.5 h): 307 ([M + 1]<sup>+</sup>, 0.07%), 291 (90), 231 (22), 216 (36), 203 (40), 185 (18), 145 (60), 131 (69), 117 (58), 103 (88), 73 (100), 59 (14), 43 (11). (Found: C, 51.9; H, 8.8. C<sub>7</sub>H<sub>14</sub>O<sub>4</sub> requires: C, 51.8; H, 8.7%).

**(2R,3R)-4-(tert-Butyldimethylsilyloxy)-2,3-(isopropylidenedioxy)butanol (13)**. Sodium hydride (0.66 g, 27.5 mmol; as 60% dispersion in mineral oil) was added portionwise to a stirred solution of D-(–)-threitol acetonide **12** (4.006 g, 24.70 mmol) in anhydrous THF (150 mL) cooled to 0 °C under Ar flow. When effervescence ceased, a solution of *tert*-butyldimethylsilyl chloride (4.105 g, 27.2 mmol) in dry THF (50 mL) was slowly added dropwise to the slurry at rt and stirred vigorously overnight under Ar atmosphere. The milky mixture was poured in water (120 mL), the yellow clear organic phase was separated and the aqueous layer extracted with ethyl acetate (3 × 50 mL). The organic phases were combined, washed with water (100 mL), dried (MgSO<sub>4</sub>) and rotary evaporated, giving a yellow residue which was chromatographed on silica gel (light petroleum–ethyl acetate from 90 : 10 to 50 : 50) to afford the desired monosilylated alcohol **13** (6.21 g, 91%) as a lemon yellow oil, [ $\alpha$ ]<sub>D</sub> –16.1 (*c* 3.2) [lit.,<sup>19,21</sup> (2*S*,3*S*) +16.1;<sup>19</sup> +15.3<sup>21</sup>]. <sup>1</sup>H NMR (200 MHz):  $\delta$  0.06 (6H, s, 2 × <sup>t</sup>BuMe<sub>2</sub>Si), 0.88 (9H, s, 3 × <sup>t</sup>BuMe<sub>2</sub>Si), 1.37 (3H, s, Me<sub>2</sub>C), 1.39 (3H, s, Me<sub>2</sub>C), 2.55 (1H, t, *J* 6.0, OH), 3.60 (6H, m, 2 × CH and 2 × CH<sub>2</sub>). <sup>13</sup>C NMR:  $\delta$  –4.19, –4.16, 19.6, 27.2, 28.2, 28.4, 64.1, 65.1, 79.4, 81.4, 110.4. MS, *m/z*: 275 ([M – 1]<sup>+</sup>, 0.07%), 261 (17), 245 (2.8), 219 (14), 201 (3.5), 187 (4.6), 173 (5.6), 161 (44), 143 (20), 131 (100), 117 (43), 105 (16), 89 (14), 75 (96), 59 (41), 43 (18). (Found: C, 56.4; H, 10.3. C<sub>13</sub>H<sub>28</sub>O<sub>4</sub>Si requires: C, 56.5; H, 10.2%).

**(2*S*,3*R*)-4-(tert-Butyldimethylsilyloxy)-2,3-(isopropylidenedioxy)butanal (14)**. Oxalyl chloride (588  $\mu$ L, 6.84 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (13 mL) in a three-necked 100-mL round bottom flask equipped with two dropping funnels and a bubbler, and treated at –80 °C with a solution of anhydrous DMSO (970  $\mu$ L, 13.68 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4.5 mL), which was added dropwise over 15 min. The milky solution thus obtained was stirred at –72 °C under Ar flow for an additional 30 min. Alcohol **13** (1.716 g, 6.22 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (8 mL) and slowly added at –70 °C over a 15 min period. After stirring at –60 °C for a further 40 min, freshly distilled anhydrous triethylamine (4.33 mL, 31.08 mmol) was added, and the reaction mixture was stirred for 15 min at the same temperature. The cold bath was then removed, the mixture allowed to warm to rt and poured in 30 mL water. The lower organic layer was separated and the aqueous phase extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL); the pooled organic layers were washed with saturated NH<sub>4</sub>Cl, satd. NaHCO<sub>3</sub> and brine (60 mL each), and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration *in vacuo* a yellow sticky oil was obtained (1.53 g, 90%).

After being repeatedly treated with anhydrous toluene and rotary evaporated in order to remove azeotropically any trace of water left, this crude material was directly used in the next step. <sup>1</sup>H NMR (200 MHz):  $\delta$  0.08 (3H, s, <sup>t</sup>BuMe<sub>2</sub>Si), 0.09 (3H, s, <sup>t</sup>BuMe<sub>2</sub>Si), 0.91 (9H, s, 3 × <sup>t</sup>BuMe<sub>2</sub>Si), 1.41 (3H, s, Me<sub>2</sub>C), 1.42 (3H, s, Me<sub>2</sub>C), 3.66–4.16 (3H, m, CHCH<sub>2</sub> and CH<sub>2</sub>), 4.33 (1H, dd, *J* 7.2, 1.6, CHCHO), 9.78 (1H, d, *J* 1.6, CHO). MS, *m/z*: 259 ([M – 15]<sup>+</sup>, 4.9%), 245 (9.5), 217 (13), 199 (4.2), 187 (7.2), 171 (4.0), 159 (5.0), 145 (6.7), 131 (60), 117 (100), 101 (60), 89 (16), 75 (75), 59 (25), 43 (18).

**(2*E*,4*R*,5*R*)- and (2*Z*,4*R*,5*R*)-6-(tert-Butyldimethylsilyloxy)-4,5-(isopropylidenedioxy)hex-2-enoic acid ethyl ester (15)**. The crude aldehyde **14** (1.189 g, 4.33 mmol) was dissolved in anhydrous DMF (36 mL) and (ethoxycarbonylmethylene)triphenylphosphorane (4.448 g, 12.77 mmol) was added portionwise at rt. The mixture was stirred overnight, poured in 350 mL water and thoroughly extracted with light petroleum (5 × 150 mL). After drying over MgSO<sub>4</sub>, filtration and evaporation under reduced pressure, the residue was purified by silica gel chromatography using light petroleum–diethyl ether 70 : 30 as the eluant, to afford the title alkene **15** in an 85 : 15 *trans*–*cis* mixture (as determined by GC-MS analysis) as a light yellow liquid (1.402 g, 94%). (Found: C, 59.5; H, 9.5. C<sub>17</sub>H<sub>32</sub>O<sub>5</sub>Si requires: C, 59.3; H, 9.4%).

**(2*E*,4*R*,5*R*)-(15)**. <sup>1</sup>H NMR (200 MHz):  $\delta$  0.07 (6H, s, 2 × <sup>t</sup>BuMe<sub>2</sub>Si), 0.90 (9H, s, 3 × Me<sub>2</sub><sup>t</sup>BuSi), 1.29 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.42 (6H, s, 2 × Me<sub>2</sub>C), 3.69–3.86 (3H, m, *H*-5 and 2 × *H*-6), 4.20 (2H, q, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 4.45–4.56 (1H, m, *H*-4), 6.12 (1H, dd, *J* 15.7, 1.6, *H*-2), 6.94 (1H, dd, *J* 15.7, 5.1, *H*-3). <sup>13</sup>C NMR:  $\delta$  –4.13, –4.07, 15.6, 19.6, 27.2, 28.1, 28.3, 61.8, 64.1, 79.2, 82.1, 111.2, 123.3, 146.0, 176.7. MS, *m/z*: 329 ([M – 15]<sup>+</sup>, 13%), 299 (7.3), 281 (5.9), 241 (4.0), 229 (100), 199 (20), 183 (34), 155 (34), 117 (36), 109 (51), 89 (41), 84 (29), 75 (74), 59 (21), 43 (18).

**(2*Z*,4*R*,5*R*)-(15)**. <sup>1</sup>H NMR (200 MHz):  $\delta$  0.057 (3H, s, <sup>t</sup>BuMe<sub>2</sub>Si), 0.061 (3H, s, <sup>t</sup>BuMe<sub>2</sub>Si), 0.88 (9H, s, 3 × <sup>t</sup>BuMe<sub>2</sub>Si), 1.28 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.43 (6H, s, 2 × Me<sub>2</sub>C), 3.69–3.86 (3H, m, *H*-5 and 2 × *H*-6), 4.17 (2H, q, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 4.76–4.84 (1H, m, *H*-4), 5.91 (1H, dd, *J* 11.7, 1.0, *H*-2), 6.18 (1H, dd, *J* 11.7, 8.6, *H*-3). <sup>13</sup>C NMR:  $\delta$  –4.0, 27.3, 28.4, 28.5, 61.7, 65.2, 75.0, 83.6, 111.3, 124.2, 146.9, (C=O not seen). MS, *m/z*: 329 ([M – 15]<sup>+</sup>, 4.3%), 287 (26), 269 (24), 241 (17), 229 (91), 199 (9.2), 183 (68), 155 (34), 117 (52), 109 (100), 89 (15), 84 (23), 75 (62), 59 (20), 43 (18).

**(4*R*,5*R*)-6-(tert-Butyldimethylsilyloxy)-4,5-(isopropylidenedioxy)hexanoic acid ethyl ester (16)**. Alkene **15** (1.321 g, 3.84 mmol) was dissolved in absolute EtOH (20 mL) and stirred overnight with 10% wt. dry Pd on C (200 mg) at rt under H<sub>2</sub> balloon pressure. The reaction mixture was passed through a short Celite plug, washing with diethyl ether and EtOH, and the resulting clear solution was evaporated to dryness to afford **16** as a colourless liquid (1.31 g, 99%) which was used as such for the next reaction. For analysis, a small sample was purified by silica gel chromatography, using light petroleum–diethyl ether 80 : 20 as the eluant; [ $\alpha$ ]<sub>D</sub> +5.9 (*c* 1.5). <sup>1</sup>H NMR (200 MHz):  $\delta$  0.07 (6H, s, 2 × <sup>t</sup>BuMe<sub>2</sub>Si), 0.89 (9H, s, 3 × <sup>t</sup>BuMe<sub>2</sub>Si), 1.25 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.36 (3H, s, Me<sub>2</sub>C), 1.38 (3H, s, Me<sub>2</sub>C), 1.75–2.14 (2H, m, 2 × *H*-3), 2.34–2.60 (2H, m, 2 × *H*-2), 3.63–3.82 (3H, m, *H*-4 and 2 × *H*-6), 3.85–3.95 (1H, m, *H*-5), 4.13 (2H, q, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta$  –4.12, –4.06, 15.6, 19.7, 27.2, 28.3, 28.8, 28.9, 32.1, 61.6, 65.0, 79.3, 82.2, 110.0, 174.6. MS, *m/z*: 345 ([M – 1]<sup>+</sup>, 0.1%), 331 (36), 301 (13), 289 (33), 271 (36), 243 (42), 231 (90), 185 (100), 157 (35), 143 (73), 111 (93), 83 (27), 75 (48), 59 (15), 43 (12). (Found: C, 59.2; H, 10.1. C<sub>17</sub>H<sub>34</sub>O<sub>5</sub>Si requires: C, 58.9; H, 9.9%).

**(4*R*,5*R*)-6-Hydroxy-4,5-(isopropylidenedioxy)hexanoic acid ethyl ester (17)**. Silylated alcohol **16** (1.26 g, 3.64 mmol) was

dissolved in anhydrous THF (10 mL) and treated with a solution of tetra-*n*-butylammonium fluoride (1.142 g, 4.37 mmol) in 6 mL THF at rt under magnetic stirring and Ar atmosphere. After 5 h the solvent was rotary evaporated, the yellowish residue dissolved in ethyl acetate (15 mL) and washed with water (15 mL). The aqueous layer was extracted with EtOAc (15 mL) and the pooled organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered. Concentration *in vacuo* followed by chromatography on silica gel (light petroleum–diethyl ether, from 70 : 30 to 40 : 60) yielded free alcohol **17** as a pale yellow oil (689 mg, 82%), [ $\alpha$ ]<sub>D</sub> +24.8 (*c* 1.1) [lit.,<sup>21,25</sup> (4*S*,5*S*) –24.1;<sup>25</sup> –19.5<sup>21</sup>]. <sup>1</sup>H NMR (200 MHz):  $\delta$  1.26 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.39 (3H, s, Me<sub>2</sub>C), 1.40 (3H, s, Me<sub>2</sub>C), 1.70–2.06 (2H, m, 2 × *H*-3), 2.10 (1H, t, *J* 5.4, OH), 2.42 (1H, ddd, *J* 16.4, 8.2, 7.0, *H*-2), 2.54 (1H, ddd, *J* 16.4, 8.4, 6.7, *H*-2), 3.59–3.68 (1H, m, *H*-5), 3.70–3.85 (2H, m, 2 × *H*-6), 3.91 (1H, dt, *J* 3.8, 7.9, *H*-4), 4.14 (2H, q, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta$  15.5, 28.4, 28.6, 29.4, 32.0, 61.8, 63.3, 77.6, 82.4, 110.3, 174.6. MS, *m/z*: 217 ([M – 15]<sup>+</sup>, 62%), 187 (7.3), 171 (8.9), 156 (7.0), 143 (23), 129 (40), 115 (45), 111 (67), 101 (22), 83 (44), 59 (100). (Found: C, 56.8; H, 8.9. C<sub>11</sub>H<sub>20</sub>O<sub>5</sub> requires: C, 56.9; H, 8.7%).

**(4*R*,5*S*)-4,5-(Isopropylidenedioxy)-6-oxohexanoic acid ethyl ester (18)**. By analogy to the preparation of aldehyde **14** described above, a solution of DMSO (404  $\mu$ L, 5.70 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was carefully added dropwise under Ar flow over a 3 min period to a stirred solution of oxalyl chloride (245  $\mu$ L, 2.85 mmol) in the same solvent (5.5 mL) cooled at –76 °C. The mixture was allowed to react for 30 min at the same temperature, until a milky turbid appearance was observed. Thereafter, alcohol **17** (601 mg, 2.59 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (3.5 mL) and slowly added at –72 °C to the white mixture over a 15 min period. After stirring for 1 h at –65 °C under Ar flow, anhydrous triethylamine (1.8 mL, 12.95 mmol) was added dropwise at –61 °C. The reaction mixture was stirred for 15 min at the same temperature, left to warm to rt over 2 h and poured into 15 mL water. The whitish clear bottom phase was separated from the aqueous layer, which was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 mL); the organic phases were combined, washed with 1 M HCl (50 mL), saturated NaHCO<sub>3</sub> (50 mL) and brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated under reduced pressure to give the crude aldehyde **18** as a lemon yellow thick oil (455 mg, 76%), which was used for the next Wittig reaction without further purification, except for repeated treatments with anhydrous toluene followed by rotary evaporation. <sup>1</sup>H NMR (200 MHz):  $\delta$  1.26 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.39 (3H, s, Me<sub>2</sub>C), 1.41 (3H, s, Me<sub>2</sub>C), 1.81–2.14 (2H, m, 2 × *H*-3), 2.38–2.60 (2H, m, 2 × *H*-2), 3.63–3.93 (1H, m, *H*-4), 3.98 (1H, dd, *J* 7.5, 2.1, CHCHO), 4.14 (2H, q, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 9.74 (1H, d, *J* 2.1, CHO). MS, *m/z*: 215 ([M – 15]<sup>+</sup>, 32%), 201 (13), 185 (30), 143 (70), 127 (33), 115 (100), 99 (26), 85 (50), 59 (23), 43 (70).

**(4*R*,5*R*)-4,5-(Isopropylidenedioxy)hept-6-enoic acid ethyl ester (19)**. Methyltriphenylphosphonium bromide (1.837 g, 5.14 mmol) was slurried in 45 mL freshly distilled anhydrous THF. The white suspension was cooled to –23 °C and *n*-butyllithium (1.2 mL of a 2.5 M solution in hexanes) was added over 2 min under Ar flow and magnetic stirring. The bright yellow mixture was vigorously stirred and allowed to warm to rt for 1 h 40 min; gas bubbles were observed to develop and a white solid to settle. The crude aldehyde **18** (438 mg, 1.90 mmol) was dissolved in dry THF (5 mL) and added dropwise over a 3 min period to the yellow slurry at –20 °C and stirred for 30 min at the same temperature. After 2 h at rt, the orange-yellow cloudy mixture was poured in 200 mL diethyl ether and stirred for 5 min; the white suspension thus formed was passed through a short Celite pad and washed with abundant ether to obtain a clear colourless solution. Concentration *in vacuo* provided a crude residue which was purified by silica gel chromatography (light

petroleum–diethyl ether 70 : 30 and finally 60 : 40) to afford the title alkene **19** (181 mg, 42%) as a yellow liquid, [ $\alpha$ ]<sub>D</sub> +0.7 (*c* 0.8). [lit.,<sup>25</sup> (4*S*,5*S*) 0]. <sup>1</sup>H NMR (200 MHz):  $\delta$  1.26 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.41 (6H, s, 2 × Me<sub>2</sub>C), 1.73–2.06 (2H, m, 2 × *H*-3), 2.33–2.61 (2H, m, 2 × *H*-2), 3.70 (1H, dt, *J* 8.2, 3.9, *H*-4), 4.01 (1H, ddt, *J* 8.2, 7.2, 0.8, *H*-5), 4.14 (2H, q, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 5.27 (1H, ddd, *J* 10.1, 1.5, 0.8, CH=CH<sub>2</sub>), 5.38 (1H, ddd, *J* 17.1, 1.5, 0.8, CH=CH<sub>2</sub>), 5.81 (1H, ddd, *J* 17.1, 10.1, 7.2, CH=CH<sub>2</sub>). <sup>13</sup>C NMR:  $\delta$  15.6, 28.2, 28.3, 28.6, 32.0, 61.8, 80.9, 83.8, 110.2, 120.6, 136.4, 174.5. MS, *m/z*: 213 ([M – 15]<sup>+</sup>, 21%), 195 (0.6), 171 (9.9), 125 (100), 115 (5.5), 98 (66), 83 (34), 69 (32), 55 (21), 43 (61). (Found: C, 63.2; H, 8.7. C<sub>12</sub>H<sub>20</sub>O<sub>4</sub> requires: C, 63.1; H, 8.8%).

**(4*R*,5*R*)-4,5-(Isopropylidenedioxy)hept-6-enoic acid (20)**. The ester **19** (166 mg, 0.728 mmol) was dissolved in 8 mL THF–MeOH (1 : 1) and treated with aqueous KOH (248 mg in 2 mL) at rt under magnetic stirring. After 2.5 h TLC (diethyl ether–light petroleum 80 : 20) showed disappearance of the starting material. The pale yellow reaction mixture was poured in a separating funnel with water and diethyl ether (80 mL each), and the pH was adjusted to 4–5 with 10% HCl. The aqueous layer was further extracted with ether (3 × 20 mL) and the pooled organic phases were washed with water (2 × 100 mL) and brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. Finally, rotary evaporation afforded the desired free acid **20** as a sticky greenish oil (118 mg, 81%), which was used as such for the next DCC-mediated coupling step. <sup>1</sup>H NMR (200 MHz):  $\delta$  1.41 (6H, s, 2 × Me<sub>2</sub>C), 1.70–2.06 (2H, m, 2 × *H*-3), 2.39–2.68 (2H, m, 2 × *H*-2), 3.72 (1H, dt, *J* 8.1, 3.9, *H*-4), 4.02 (1H, dd, *J* 8.1, 7.3, *H*-5), 5.27 (1H, ddd, *J* 10.2, 1.5, 0.8, CH=CH<sub>2</sub>), 5.38 (1H, ddd, *J* 17.2, 1.5, 0.9, CH=CH<sub>2</sub>), 5.81 (1H, ddd, *J* 17.2, 10.2, 7.3, CH=CH<sub>2</sub>). <sup>13</sup>C NMR:  $\delta$  26.5, 26.9, 27.1, 30.3, 79.4, 82.4, 108.9, 119.1, 135.0, 178.7. MS, *m/z*: 200 (M<sup>+</sup>, 0.1%), 185 (64), 167 (1.4), 144 (5.1), 125 (100), 98 (93), 83 (57), 69 (47), 55 (28), 43 (84). (Found: C, 60.2; H, 7.8. C<sub>10</sub>H<sub>16</sub>O<sub>4</sub> requires: C, 60.0; H, 8.0%).

#### DCC-mediated coupling and final steps of the total synthesis

**(4*R*,5*R*)-4,5-(Isopropylidenedioxy)hept-6-enoic acid, (1'*S*,1''*S*)-1'-(1''-benzyloxyheptyl)-3'-butenyl ester (21)**. A solution of acid **20** (118 mg, 0.590 mmol) in 1.5 mL anhydrous ether was added dropwise to alcohol **9** (165 mg, 0.598 mmol) in dry ether (2 mL), and DCC (122 mg, 0.590 mmol) was added at rt, along with DMAP (7 mg, 0.057 mmol). After stirring for 5.5 h, the white precipitate was filtered off and the yellow clear solution evaporated to dryness. The turbid yellow oil was chromatographed on silica gel with light petroleum–diethyl ether 95 : 5 to afford ester **21** as a liquid (205 mg, 85%), [ $\alpha$ ]<sub>D</sub> –1.9 (*c* 4.2), along with 19 mg of unreacted **9**. <sup>1</sup>H NMR (200 MHz):  $\delta$  0.89 (3H, t, *J* 6.5, 3 × *H*-7''), 1.26 (8H, br m, *H*-3'' to *H*-6''), 1.39 (3H, s, Me<sub>2</sub>C), 1.41 (3H, s, Me<sub>2</sub>C), 1.44–1.62 (2H, m, 2 × *H*-2''), 1.72–2.07 (2H, m, 2 × *H*-3), 2.17–2.62 (4H, m, 2 × *H*-2 and 2 × *H*-2'), 3.45 (1H, dt, *J* 7.1, 4.5, *H*-1''), 3.69 (1H, dt, *J* 8.1, 3.9, *H*-4), 4.00 (1H, dd, *J* 8.1, 7.2, *H*-5), 4.60 (2H, s, CH<sub>2</sub>Ph), 4.97–5.18 (3H, m, *H*-1' and 2 × *H*-4'), 5.25 (1H, ddd, *J* 10.2, 1.5, 0.8, *H*-7), 5.38 (1H, ddd, *J* 17.1, 1.5, 0.9, *H*-7), 5.63–5.79 (1H, m, *H*-3'), 5.80 (1H, ddd, *J* 17.1, 10.2, 7.2, *H*-6), 7.23–7.40 (5H, m, arom). <sup>13</sup>C NMR:  $\delta$  14.0, 22.5, 25.5, 26.9, 27.2, 29.3, 29.9, 30.8, 31.7, 34.4, 72.4, 73.5, 79.0, 82.4, 108.8, 117.5, 118.9, 127.6, 127.8, 128.3, 134.1, 135.1, 138.5, 172.6. MS, *m/z*: 458 (M<sup>+</sup>, 0.4%), 443 (0.8), 361 (0.8), 294 (11), 275 (3.5), 259 (5.6), 223 (3.8), 205 (11), 183 (6.8), 143 (9.7), 125 (70), 98 (35), 91 (100), 83 (10), 69 (9.2), 55 (9.0), 43 (12). (Found: C, 73.4; H, 9.1. C<sub>28</sub>H<sub>42</sub>O<sub>5</sub> requires: C, 73.3; H, 9.2%).

**(5*R*,6*R*,7*E*,10*S*)- and (5*R*,6*R*,7*Z*,10*S*)-10-[(1'*S*)-1'-Benzyloxyheptyl]-5,6-isopropylidenedioxy-3,4,5,6,9,10-hexahydro-2*H*-oxecin-2-one, (*E*-**22** and *Z*-**22**)**. Ester **21** (50 mg, 0.109 mmol) was dissolved in freshly distilled degassed anhydrous CH<sub>2</sub>Cl<sub>2</sub>



(230 mL) and Grubbs' catalyst **I** was added (15.5 mg, 0.0188 mmol). The mixture was refluxed for 2 days under Ar flow until TLC (light petroleum–diethyl ether 80 : 20) showed complete disappearance of the starting material. Most of the solvent was then distilled off and the concentrated solution left to stir at rt for 2 h under air bubbling in order to decompose the catalyst. Evaporation to dryness gave a brown residue which was purified by chromatography on silica gel; slow elution with light petroleum–diethyl ether mixtures (from 97 : 3 to 80 : 20) allowed separation of the desired *trans* stereoisomer (*E*)-**22** (29 mg) from *cis* derivative (*Z*)-**22** (14 mg) (combined 92% yield).

(5*R*,6*R*,7*E*,10*S*)-**22**. [ $\alpha$ ]<sub>D</sub> –37.9 (*c* 3.0). <sup>1</sup>H NMR (200 MHz):  $\delta$  0.90 (3H, t, *J* 6.5, 3 × *H*-7'), 1.27 (8H, br envelope, *H*-3' to *H*-6'), 1.41 (6H, s, 2 × *Me*<sub>2</sub>C), 1.51–1.80 (2H, m, 2 × *H*-2'), 1.87–2.71 (6H, m, 2 × *H*-3, *H*-4 and *H*-9), 3.47 (1H, m, *H*-1'), 3.64 (1H, m, *H*-5), 3.92 (1H, t, *J* 9.2, *H*-6), 4.56 (1H, d, *J* 11.6, *CH*<sub>2</sub>Ph), 4.65 (1H, d, *J* 11.6, *CH*<sub>2</sub>Ph), 4.95 (1H, m, *H*-10), 5.32 (1H, dd, *J* 15.6, 9.2, *H*-7), 5.78 (1H, ddd, *J* 15.6, 11.0, 4.7, *H*-8), 7.29–7.40 (5H, m, arom). <sup>13</sup>C NMR:  $\delta$  14.0, 22.5, 25.4, 25.6, 26.9, 27.1, 29.4, 29.7, 31.7, 34.2, 72.5, 73.4, 79.8, 80.4, 84.4, 108.8, 127.8, 127.9, 128.4, 129.2, 130.3, 138.2, 171.8. MS, *m/z*: 430 (M<sup>+</sup>, 0.22%), 415 (0.33), 373 (0.60), 328 (1.1), 298 (0.71), 237 (3.3), 220 (1.8), 205 (4.3), 203 (7.0), 179 (1.8), 123 (6.2), 113 (14), 91 (100), 85 (23), 79 (6.2), 65 (3.1), 55 (5.5). (Found: C, 72.4; H, 9.0. C<sub>26</sub>H<sub>38</sub>O<sub>5</sub> requires: C, 72.5; H, 8.9%).

(5*R*,6*R*,7*Z*,10*S*)-**22**. [ $\alpha$ ]<sub>D</sub> +4.5 (*c* 1.6). <sup>1</sup>H NMR (200 MHz):  $\delta$  0.89 (3H, t, *J* 6.5, 3 × *H*-7'), 1.27 (8H, br envelope, *H*-3' to *H*-6'), 1.40 (3H, s, *Me*<sub>2</sub>C), 1.42 (3H, s, *Me*<sub>2</sub>C), 1.50–1.77 (2H, m, 2 × *H*-2'), 2.01–2.77 (6H, m, 2 × *H*-3, *H*-4 and *H*-9), 3.49 (1H, m, *H*-1'), 3.66 (1H, ddd, *J* 10.2, 9.5, 2.3, *H*-5), 4.52 (1H, dd, *J* 9.5, 8.0, *H*-6), 4.58 (1H, d, *J* 11.6, *CH*<sub>2</sub>Ph), 4.66 (1H, d, *J* 11.6, *CH*<sub>2</sub>Ph), 5.10 (1H, ddd, *J* 11.8, 4.4, 2.2, *H*-10), 5.50 (1H, t, *J* 10.3, *H*-7), 5.74 (1H, dt, *J* 10.3, 7.0, *H*-8), 7.28–7.44 (5H, m, arom). <sup>13</sup>C NMR:  $\delta$  14.0, 22.5, 25.4, 26.8, 27.0, 29.3, 29.6, 30.5, 31.7, 32.1, 72.6, 72.8, 77.1, 79.7, 81.5, 107.6, 127.7, 128.4, 130.3, 130.9, 138.0, 176.6. MS, *m/z*: 430 (M<sup>+</sup>, 0.69%), 415 (2.3), 373 (0.30), 328 (1.1), 298 (0.60), 265 (1.7), 237 (3.0), 220 (1.7), 205 (3.9), 203 (6.3), 179 (2.5), 123 (5.1), 113 (13), 91 (100), 85 (16), 79 (6.6), 65 (3.1), 55 (6.6). (Found: C, 72.7; H, 9.1. C<sub>26</sub>H<sub>38</sub>O<sub>5</sub> requires: C, 72.5; H, 8.9%).

(5*R*,6*R*,7*E*,10*S*)-**5,6-Dihydroxy-10-[(1'*S*)-1'-hydroxyheptyl]-3,4,5,6,9,10-hexahydro-2*H*-oxecin-2-one (microcarpalide, **1**)<sup>3</sup>. Titanium tetrachloride (66  $\mu$ L, 0.605 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) was slowly added dropwise over 10 min to a stirred solution of *trans* derivative *E*-**22** (26 mg, 0.0605 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) cooled to 0 °C. After 1.5 h the ochre-yellow cloudy mixture was poured in water (5 mL), diluted with CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and treated with satd. NaHCO<sub>3</sub> (8 mL), brine (5 mL) and EtOAc (15 mL) in a separating funnel. After settling, the upper milky layer was discarded, whereas the clear lower phase was separated, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure; silica gel chromatography of the crude residue using ethyl acetate as the eluant afforded microcarpalide **1** as a beige oil (12 mg, 66%), [ $\alpha$ ]<sub>D</sub> –23.6 (*c* 1.0, MeOH) (lit.<sup>3</sup> –22). NMR analysis clearly showed the presence of two slowly interconverting conformers in a 76 : 24 ratio (in CD<sub>3</sub>CN), which is identical to the value described in the literature for the natural compound in the same solvent.<sup>3</sup> <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN; referenced to the residual proton at 1.96 ppm):  $\delta$  0.91 (3H, t, *J* 6.8, 3 × *H*-7'), 1.26–1.38 (8H, br envelope, *H*-3' to *H*-6'), 1.41–1.47 (2H, br m, 2 × *H*-2'), 1.80 (1H, br dddd, *H*-4), 2.02 (1H, br ddd, *H*-4 minor conformer), 2.11–2.23 (3H, br m, *H*-3, *H*-4 and *H*-9), 2.27–2.34 (1H, br m, *H*-9), 2.36 (1H, ddd, *J* 5.2, 2.7, 1.1, *H*-9 minor), 2.47–2.58 (1H, m, *H*-3), 2.83 (1H, d, *J* 5.8, 1'-OH), 2.86 (1H, d, *J* 6.4, 6-OH), 3.09 (1H, d, *J* 4.1, 5-OH), 3.19 (1H, d, *J* 3.2, 5-OH minor), 3.28 (1H, br dt, *H*-5 minor), 3.54–3.60 (1H, br m, *H*-1'), 3.64 (1H, dt, *J* 3.1, 9.1, *H*-6 minor), 3.80 (1H, br m, *H*-5), 4.13 (1H, br m, *H*-6), 4.63 (1H, ddd, *J* 8.4, 4.5, 2.7, *H*-10 minor), 4.84 (1H, ddd,**

*J* 11.3, 4.9, 3.3, *H*-10), 5.08 (1H, dd, *J* 15.7, 9.4, *H*-7 minor), 5.53 (1H, dddd, *J* 15.8, 10.3, 5.3, 2.2, *H*-8), 5.69 (1H, m, *H*-8 minor), 5.73 (1H, dd, *J* 15.8, 2.5, *H*-7). <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>CN; referenced to CD<sub>3</sub>CN at 118.26 ppm):  $\delta$  14.4 (*C*-7'), 23.3 (*C*-6'), 26.1 (*C*-3'), 26.5 (*C*-4), 29.3 (*C*-3), 30.0 (*C*-4'), 32.2 (*C*-9, minor conformer), 32.3 (*C*-5', minor), 32.6 (*C*-5'), 33.9 (*C*-2', minor), 34.3 (*C*-2'), 35.9 (*C*-3, minor), 36.7 (*C*-9), 72.5 (*C*-6), 72.9 (*C*-1'), 73.5 (*C*-5), 73.8 (*C*-1', minor), 76.4 (*C*-10, minor), 77.0 (*C*-5, minor), 79.5 (*C*-6, minor), 79.7 (*C*-10), 126.7 (*C*-8), 130.0 (*C*-8, minor), 133.8 (*C*-7, minor), 134.6 (*C*-7), 173.5 (*C*-2, minor), 176.4 (*C*-2) [see also electronic supporting information (ESI) for original <sup>1</sup>H and <sup>13</sup>C NMR spectra of synthetic **1**]. MS, *m/z*: 301 ([M + 1]<sup>+</sup>, 1.4%), 283 (0.55), 265 (0.78), 198 (6.2), 180 (55), 162 (1.2), 151 (3.5), 141 (10), 129 (30), 113 (13), 110 (16), 95 (39), 84 (100), 73 (44), 70 (80), 55 (64). (Found: C, 63.9; H, 9.2. C<sub>16</sub>H<sub>28</sub>O<sub>5</sub> requires: C, 64.0; H, 9.4%).

## Acknowledgements

We are grateful to the Università di Modena e Reggio Emilia ("Progetto Giovani Ricercatori" to P.D.) for financial support. Spectroscopic assistance from the staff at Centro Interdipartimentale Grandi Strumenti (Università di Modena) has been greatly appreciated throughout the project. We thank Stefania Morandi and Chiara Danieli for critically examining NMR assignments of pinanediol boronates. We are also grateful to Dr Claudia Zucchi for kindly providing Fürstner's catalyst **III**.

## References

- (a) J. Gusman and M. Vanhaelen, *Recent Res. Dev. Phytochem.*, 2000, **4**, 187–206; (b) R.-X. Tan and W.-H. Zou, *Nat. Prod. Rep.*, 2001, **18**, 448–459; (c) B. Schulz, C. Boyle, S. Draeger, A. K. Rommert and K. Krohn, *Mycol. Res.*, 2002, **106**, 996–1004.
- For recent examples: (a) D. B. Stierle, A. A. Stierle and T. Bugni, *J. Org. Chem.*, 2003, **68**, 4966–4969; (b) G. Y. Chen, Y. C. Lin, L. Wen, L. L. P. Vrijmoed and E. B. G. Jones, *Tetrahedron*, 2003, **59**, 4907–4909; (c) J. A. Findlay, G. Q. Li, J. D. Miller and T. O. Womiloju, *Can. J. Chem.*, 2003, **81**, 284–292; (d) A. Abdel-Lateff, C. Klemke, G. M. König and A. D. Wright, *J. Nat. Prod.*, 2003, **66**, 706–708; (e) P. Kongsaree, S. Prabpai, N. Sriubolmas, C. Vongvein and S. Wiyakrutta, *J. Nat. Prod.*, 2003, **66**, 709–711; (f) B. Köpke, R. W. S. Weber and H. Anke, *Phytochemistry*, 2002, **60**, 709–714; (g) G. Strobel, E. Ford, J. Worapong, J. K. Harper, A. M. Arif, D. M. Grant, P. C. W. Fung and R. M. W. Chau, *Phytochemistry*, 2002, **60**, 179–183; (h) S. F. Brady, S. M. Bondi and J. Clardy, *J. Am. Chem. Soc.*, 2001, **123**, 9900–9901; (i) J. Y. Li, J. K. Harper, D. M. Grant, B. O. Tombe, B. Bashyal, W. M. Hess and G. A. Strobel, *Phytochemistry*, 2001, **56**, 463–468.
- A. S. Ratnayake, W. Y. Yoshida, S. L. Mooberry and T. Hemscheidt, *Org. Lett.*, 2001, **3**, 3479–3481.
- B. Bodo, L. Molho, D. Davoust and D. Molho, *Phytochemistry*, 1983, **22**, 447–451.
- (a) A. Evidente, R. Lanzetta, R. Capasso, M. Vurro and A. Bottalico, *Phytochemistry*, 1993, **34**, 999–1003; (b) A. Evidente, R. Capasso, M. A. Abouzeid, R. Lanzetta, M. Vurro and A. Bottalico, *J. Nat. Prod.*, 1993, **56**, 1937–1943.
- A. Arnone, G. Assante, M. Montorsi, G. Nasini and E. Ragg, *Gazz. Chim. Ital.*, 1993, **123**, 71–73.
- (a) A. Evidente, R. Lanzetta, R. Capasso, A. Andolfi, A. Bottalico, M. Vurro and M. C. Zonno, *Phytochemistry*, 1995, **40**, 1637–1641; (b) A. Evidente, R. Lanzetta, R. Capasso, A. Andolfi, M. Vurro and M. C. Zonno, *Phytochemistry*, 1997, **44**, 1041–1045; (c) A. Evidente, R. Capasso, A. Andolfi, M. Vurro and M. C. Zonno, *Phytochemistry*, 1998, **48**, 941–945.
- (a) J. F. Rivero-Cruz, G. García-Aguirre, C. M. Cerda-García-Rojas and R. Mata, *Tetrahedron*, 2000, **56**, 5337–5344; (b) J. F. Rivero-Cruz, M. Macías, C. M. Cerda-García-Rojas and R. Mata, *J. Nat. Prod.*, 2003, **66**, 511–514.
- Reviews: (a) T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18–29; (b) A. Fürstner, *Angew. Chem., Int. Ed.*, 2000, **39**, 3012–3043; (c) R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413–4450.
- (a) D. S. Matteson, *Acc. Chem. Res.*, 1988, **21**, 294–300; (b) D. S. Matteson, *Chem. Rev.*, 1989, **89**, 1535–1551; (c) D. S. Matteson, *J. Organomet. Chem.*, 1999, **581**, 51–65.

- 11 D. S. Matteson, K. M. Sadhu and M. L. Peterson, *J. Am. Chem. Soc.*, 1986, **108**, 810–819.
- 12 H. R. Snyder, J. A. Kuck and J. R. Johnson, *J. Am. Chem. Soc.*, 1938, **60**, 105–111.
- 13 (a) D. S. Matteson and D. Majumdar, *J. Am. Chem. Soc.*, 1980, **102**, 7588–7590; (b) D. S. Matteson and D. Majumdar, *Organometallics*, 1983, **2**, 1529–1535.
- 14 (a) M. M. Midland, A. R. Zolopa and R. L. Halterman, *J. Am. Chem. Soc.*, 1979, **101**, 248–249; (b) D. S. Matteson, *Acc. Chem. Res.*, 1970, **3**, 186–193.
- 15 (a) D. S. Matteson and R. Ray, *J. Am. Chem. Soc.*, 1980, **102**, 7590–7591; (b) D. S. Matteson, R. Ray, R. R. Rocks and D. J. Tsai, *Organometallics*, 1983, **2**, 1536–1543.
- 16 (a) H. C. Brown, in *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, 1972, pp. 317–409; (b) G. W. Kabalka, R. J. Newton, Jr. and J. Jacobus, *J. Org. Chem.*, 1978, **43**, 1567–1569.
- 17 M. Carmack and C. H. Kelley, *J. Org. Chem.*, 1968, **33**, 2171–2173.
- 18 P. W. Feit, *J. Med. Chem.*, 1964, **7**, 14–17.
- 19 J. Taunton, J. L. Collins and S. L. Schreiber, *J. Am. Chem. Soc.*, 1996, **118**, 10412–10422.
- 20 H. Iida, N. Imazaki and C. Kibayashi, *J. Org. Chem.*, 1987, **52**, 3337–3342.
- 21 S. Clough, M. E. Raggatt, T. J. Simpson, C. L. Willis, A. Whiting and S. K. Wrigley, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2475–2481.
- 22 P. Schnurrenberger, E. Hungerbühler and D. Seebach, *Liebigs Ann. Chem.*, 1987, 733–744.
- 23 During a preliminary approach to fragment **B**, diol **12** was treated with NaH and benzyl bromide in DMF at  $-40\text{ }^{\circ}\text{C}$  to afford the corresponding monobenzyl derivative.<sup>21</sup> In fact, a benzyl protection seemed convenient since it could have been removed *en route*, during the hydrogenation step that was planned to follow the first Wittig homologation. Surprisingly and unexpectedly, however, cleavage of the benzyl group by catalytic hydrogenation was found rather troublesome, even under higher pressures. Hence, annoyingly, the problem was circumvented by switching to a different protecting group for diol **12**, namely TBDMS, and the synthetic sequence had to be lengthened by one step, *i.e.*, deprotection with TBAF.
- 24 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190–6191.
- 25 (a) D. Batty and D. J. Crich, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3193–3204; (b) D. Batty and D. J. Crich, *Tetrahedron Lett.*, 1992, **33**, 875–878.
- 26 J. Murga, E. Falomir, J. García-Fortanet, M. Carda and J. A. Marco, *Org. Lett.*, 2002, **4**, 3447–3449.
- 27 A. Fürstner, K. Radkowski, C. Wirtz, R. Goddard, C. W. Lehmann and R. Mynott, *J. Am. Chem. Soc.*, 2002, **124**, 7061–7069.
- 28 D. Liu and S. A. Kozmin, *Org. Lett.*, 2002, **4**, 3005–3007.
- 29 A. Fürstner, O. Guth, A. Düffels, G. Seidel, M. Liebl, B. Gabor and R. Mynott, *Chem.-Eur. J.*, 2001, **7**, 4811–4820.
- 30 M. K. Gurjar, R. Nagaprasad and C. V. Ramana, *Tetrahedron Lett.*, 2003, **44**, 2873–2875.
- 31 E. J. Corey, J. L. Gras and P. Ulrich, *Tetrahedron Lett.*, 1976, **11**, 809–812.
- 32 M. F. Lappert, *Chem. Rev.*, 1956, **56**, 959–1064.
- 33 H. C. Brown, N. G. Bhat and V. Somayaji, *Organometallics*, 1983, **2**, 1311–1316.
- 34 L. J. Rubin, H. A. Lardy and H. O. L. Fischer, *J. Am. Chem. Soc.*, 1952, **74**, 425–428.